Broadening the debate about post-trial access to medical interventions:

AJOB Empirical Bioethics

ISSN: 2329-4515 (Print) 2329-4523 (Online) Journal homepage: https://www.tandfonline.com/loi/uabr21

Broadening the Debate About Post-trial Access to Medical Interventions: A Qualitative Study of Participant Experiences at the End of a Trial Investigating a Medical Device to Support Type 1 Diabetes Self-Management

J. Lawton, M. Blackburn, D. Rankin, C. Werner, C. Farrington, R. Hovorka & N. Hallowell

To cite this article: J. Lawton, M. Blackburn, D. Rankin, C. Werner, C. Farrington, R. Hovorka & N. Hallowell (2019): Broadening the Debate About Post-trial Access to Medical Interventions: A Qualitative Study of Participant Experiences at the End of a Trial Investigating a Medical Device to Support Type 1 Diabetes Self-Management, AJOB Empirical Bioethics, DOI: 10.1080/23294515.2019.1592264

To link to this article: https://doi.org/10.1080/23294515.2019.1592264

Published online: 15 Apr 2019.

AJOB EMPIRICAL BIOETHICS
https://doi.org/10.1080/23294515.2019.1592264

Broadening the Debate About Post-trial Access to Medical Interventions: A Qualitative Study of Participant Experiences at the End of a Trial Investigating a Medical Device to Support Type 1 Diabetes Self-Management

J. Lawton[a], M. Blackburn[a], D. Rankin[a], C. Werner[a], C. Farrington[b], R. Hovorka[c,d], and N. Hallowell[e]

[a]Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, United Kingdom; [b]Cambridge Centre for Health Services Research, University of Cambridge, United Kingdom; [c]Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, United Kingdom; [d]Department of Paediatrics, University of Cambridge, Cambridge, United Kingdom; [e]Wellcome Centre for Ethics and Humanities and the Ethox Centre, Nuffield Department of Population Health, Big Data Institute, University of Oxford, Oxford, United Kingdom

ABSTRACT

Increasing ethical attention and debate is focusing on whether individuals who take part in clinical trials should be given access to post-trial care. However, the main focus of this debate has been upon drug trials undertaken in low-income settings. To broaden this debate, we report findings from interviews with individuals ($n = 24$) who participated in a clinical trial of a closed-loop system, which is a medical device under development for people with type 1 diabetes that automatically adjusts blood glucose to help keep it within clinically recommended ranges. Individuals were recruited from UK sites and interviewed following trial close-out, at which point the closed-loop had been withdrawn. While individuals were stoical and accepting of the requirement to return the closed-loop, they also conveyed varying degrees of distress. Many described having relaxed diabetes management practices while using the closed-loop and having become deskilled as a consequence, which made reverting back to pre-trial regimens challenging. Participants also described unanticipated consequences arising from using a closed-loop. As well as deskilling, these included experiencing psychological and emotional benefits that could not be sustained after the closed-loop had been withdrawn and participants reevaluating their pre- and post-trial life in light of having used a closed-loop and now perceiving this life much more negatively. Participants also voiced frustrations about experiencing better blood glucose control using a closed-loop and then having to revert to using what they now saw as antiquated and imprecise self-management tools. We use these findings to argue that ethical debates about post-trial provisioning need to be broadened to consider potential psychological and emotional harms, and not just clinical harms, that may result from withdrawal of investigated treatments. We also suggest that individuals may benefit from information about potential nonclinical harms to help make informed decisions about trial participation.

KEYWORDS

Post-trial access; patient perspective; ethics; medical device; qualitative research

Introduction

Clinical trials rely on volunteers who should not experience unnecessary harm as a result of their participation. Hence, regulations and codes of practice have been put in place to help ensure research designs are rigorous and appropriate, that risks associated with participation are minimized, that individuals are able to make informed and voluntary decisions about taking part, and that research participants are treated with dignity and respect (Emanuel, Wendler, and Grady 2000; Grady 2005). Until relatively recently it has been assumed that the trial team's ethical, legal, and clinical responsibilities to participants stop when a trial comes to an end (Cook, Snyder, and Calvert 2016; Grady 2005). However, increasing attention and debate are focusing on whether individuals should be given access to post-trial care (Cook, Snyder, and Calvert 2016; Doval, Shirali, and Sinha 2015; El Setouhy et al. 2002; Merritt and Grady 2006; Pratt and Loff 2011; Usharani and Naqvi 2013). This

CONTACT J. Lawton J.Lawton@ed.ac.uk Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Old Medical School, Teviot Place, Edinburgh EH8 9AG, United Kingdom.

attention has been prompted by the globalization of clinical trial research and, more specifically, the growing involvement of individuals from low-income settings in pharmaceutical trials (Cook, Snyder, and Calvert 2016; Petryna 2009). Particular concern has been expressed about the ethics of allowing such individuals to shoulder the risks and burdens of trial participation when the beneficiaries tend to be companies and individuals in the developed world (Cook, Snyder, and Calvert 2016; Macklin 2004; Millum 2011). To avoid potential exploitation, and to fulfill an ethic of beneficence and reciprocity, it has been argued that there is a moral and ethical imperative to give individuals, who could not otherwise afford them, ongoing access to trial (drug) treatments if these are shown to be effective (Cook, Snyder, and Calvert 2016; Millum 2011). Such an imperative is seen to be heightened in situations where withdrawal of drug therapy might result in the worsening of an individual's condition, or possibly even death (Doval, Shirali, and Sinha 2015; Grady 2005) and, hence, where the basic tenet of human dignity might be violated (Andanda and Wathuta 2018).

Indeed, it was in response to the kinds of concerns just described that, in 2000, the Declaration of Helsinki mandated that "at the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by the study" (World Medical Association 2000, 3045). Similar recommendations for post-trial access to products and procedures of proven efficacy have also been made by other organizations (e.g., UNAIDS: Joint United Nations Programme on HIV/AIDS 2011; World Health Organization and Council for International Organizations of Medical Sciences 2016). While these kinds of guidelines have been welcomed, concern has also been expressed about the ethics of providing post-trial treatment to individuals if this means depriving those who have greater clinical need (Usharani and Naqvi 2013). Hence, some commentators have proposed that a fair-benefits framework be adopted, wherein research teams work in collaborative partnership with target populations in developing communities and allow these communities to decide how the benefits of the research are distributed (El Setouhy et al. 2002). In such cases, a fair benefit might not simply be ongoing access to the investigated treatment; it could also be achieved through other means, such as investment in the local health infrastructure (Ballantyne 2008; El Setouhy et al. 2002). However, it has also been noted that a requirement to offer post-trial care (or equivalent investment in the host community) will escalate the costs of research and mean fewer trials are conducted. Hence, commentators have observed that the ethics of providing post-trial access are far from straightforward (Doval, Shirali, and Sinha 2015; Grady 2005).

To date, ethical attention and debate have overwhelmingly focused on trials undertaken in low-income settings and on drug trials in particular (Cook, Snyder, and Calvert 2016; Sofaer and Strech 2011). As some commentators have noted, this has potentially meant that participants' need for medical interventions at the end of other kinds of trials, including those undertaken in high-income settings, might have been sidelined (Andanda and Wathuta 2018; Millum 2011; Sofaer et al. 2009). Others have argued that trial research undertaken in high-income settings is likely to be less ethically contentious. This is because if a trialed intervention is shown to be efficacious, there is a high probability that it will be introduced into the health care system and, hence, made available to at least some citizens (Pratt and Loff 2011)

Despite the emphasis placed on treating trial participants in fair and ethical ways, it is noteworthy that these individuals have rarely been consulted about the care and support they feel they need at the end of a trial. In rare instances where consultation has taken place, drug trials have been the focus of the research, with participants generally endorsing post-trial drug provisioning, especially when individuals might otherwise be unable to afford treatments (Pace et al. 2006; Shaffer et al. 2006). Currently missing from the literature is consideration of what should happen at the end of trials involving withdrawal of technologies/medical devices rather than drugs, as distinctive ethical challenges might arise and specific considerations may be needed to help address these. Arguably, this kind of work is both pressing and timely, because trials of medical devices are becoming increasingly common and widespread, especially in the field of diabetes research (Bekiari et al. 2018; Poolsup, Suksomboon, and Kyaw 2013).

To address a lacuna in the literature and expand, and potentially advance, debates about post-trial provisioning, we report findings from a qualitative study involving individuals who took part in an open-label, multicenter, randomized trial that sought to test the safety and efficacy of a closed-loop system as compared to sensor-augmented pump therapy (an open-loop system that is commercially available) in adults and youth (aged 6 years and over) who had type 1 diabetes. A closed-loop system is a medical device under development for people who have type 1 diabetes, which is a chronic disease that occurs when the

pancreas is unable to produce insulin. Hence, individuals affected by this condition have to self-regulate their blood glucose and try to keep it within the "normal" range in order to remain healthy. This is because high blood glucose levels increase the risk of long-term complications (e.g., blindness, amputation and stroke), whereas low blood glucose (hypoglycemia) can lead to confusion, seizures, periods of unconsciousness, and sometimes even death. Individuals normally regulate their (or their child's) blood glucose by administering insulin (via injections or an insulin pump) and calculating and titrating doses according to the results of blood glucose checks (normally finger-prick tests undertaken 5–6 times daily), food consumed, physical activity, and other factors (e.g., illness). The closed-loop system investigated in the trial comprised an insulin pump, a continuous glucose monitoring (CGM) device that measured interstitial blood glucose every 5 min, and a computer-based algorithm that translated, in real-time, the information received from the CGM device, in order to determine the amount of insulin that was then automatically delivered by the pump. As well as improving an individual's blood glucose control, an intended purpose of closed-loop technology is to reduce the burden of self-management (Bekiari et al. 2018), although users of the specific closed-loop system investigated in the trial had to determine the amount of carbohydrates they consumed in meals/snacks and enter this information so that an appropriate amount of extra insulin could be administered (Bally et al. 2017).

The trial used a 1:1 randomization procedure. To be eligible for the trial, individuals needed to have been using an insulin pump for at least 3 months and to have had suboptimal blood glucose control (Bally et al. 2017). During the trial, participants attended up to 11 in-clinic visits and had six preplanned telephone contacts (Bally et al. 2017). Following trial completion, individuals were put back on to their pre-trial (i.e., insulin pump) regimen; this meant that, in practice, they had to stop using the CGM device and algorithm that automatically regulated their or their child's blood glucose. In the participant information sheet, participants were advised of the requirement to return the study devices promptly at the end of the study and that, as a last resort, the trial team would use legal measures to ensure this happened. Participants were also advised of possible risks arising from study participation, such as a low risk of hyperglycemia leading to diabetic ketoacidosis resulting from use of the closed-loop. However, the participant information sheet made no mention of any possible risks resulting from withdrawal of the closed-loop at the end of the study period.

In many respects, the study reported here is an unusual example as it drew upon the perspectives and experiences of participants who had participated a trial of a medical device (rather than a drug) that had to be withdrawn at the end as it was still under development and, hence, not yet licensed for clinical use. However, while commentators have suggested that phase I–III trials are relatively uncontroversial because "no efficacious product can be expected at the end of such trials in order to fulfill any post-trial obligation of making the product available to participants" (Andanda and Wathuta 2018) (unless a country's regulations permit a compassionate use exemption to be exercised), we will show that ethical and other considerations nonetheless exist when an investigated treatment is not available post trial.

The material reported here forms part of a broader qualitative study in which we interviewed participants following randomization to a closed-loop and within 1–2 weeks of completing the 3-month trial, at which point they had returned the closed-loop to the trial team. The main purpose of this qualitative research was to explore people's initial understandings and expectations of closed-loop systems, their likes and dislikes of using a closed loop, and their views about how the technology might be improved to increase efficacy and acceptability for future users (findings from this component of the research are reported separately: Lawton et al. 2019a, 2019b). However, after initial end-of-trial interviews alerted us to participants experiencing anxiety and distress as a result of having to return the closed-loop, a decision was made to add a bioethical expert to the qualitative research team and broaden the remit of these interviews. Specifically, we used these interviews to understand and explore the reasons for participant distress, and what, from their perspectives, might be done differently to support people who take part in future trials that require medical devices to be returned at the end of the study period. It is the findings from these aspects of the interviews that form the focus of our reporting here.

Methods

In-depth interviews informed by topic guides were used so that the discussion remained relevant to the study aims, while affording the flexibility needed for participants to raise and discuss issues they perceived as salient, including those unforeseen at the study's

outset (Pope and Mays 1995). An inductive approach was used (Strauss and Corbin 1990) in which data collection and analysis took place concurrently, allowing findings from early interviews to iteratively inform areas explored in later ones. This included our decision to broaden the remit of the end of trial interviews to understand and explore participants' reactions to withdrawal of the closed-loop in more depth.

Sample and recruitment

We interviewed adult (18+ years) and adolescent (13–17 years) trial participants and parents of trial participants aged 13–15 years and 12 years and under. The decision to interview parents was made because, among pre-teenage children, parents take overarching responsibility for diabetes management tasks and decision-making (Lawton et al. 2015), and hence it was recognized that these individuals would have primary responsibility for using the closed-loop. We also decided to interview parents of trial participants aged 13–15 years, as, in the early teenage years, youth often continue to look to their parents for input and support when undertaking diabetes self-management tasks (Williams 2000).

Participants were recruited and consented into the qualitative research at the same time that they were recruited into the trial. Recruitment was undertaken by members of the clinical team in all four participating UK trial sites using an opt-in procedure, with assent procedures used for minors (Bally et al. 2017). Data collection for the qualitative research continued until data saturation was reached—that is, until no new findings were identified in new data collected.

Data collection and analysis

MB conducted the interviews at a time and location of participants' choosing, using a topic guide that was developed in light of literature reviews and input from the co-investigator team, and revised in light of emerging findings (see preceding discussion). Key areas explored that are relevant to the reporting in this article include: perceptions and understandings of the trial; experiences of undertaking diabetes (self-) management using a closed-loop; perceived impact of using a closed-loop on oneself and others, food choices and eating practices; (physical) activity and everyday (work, school, family) life; benefits and burdens of using a closed-loop as compared to pre-trial regimens; experiences of trial close-out; reactions to withdrawal of the closed-loop (and participants' own understandings of the reasons for these); views about how close-out experiences could be improved for future trial participants; and participants' information and support needs post-trial.

Interviews took place between October 2016 and August 2017. These typically lasted 1–2 hours, and were digitally recorded and transcribed in full. Data were analyzed by a team of experienced qualitative researchers (JL, MB, DR, and CW) using a thematic approach involving cross-comparison of all interviews to identify recurrent themes (Strauss and Corbin 1990). These researchers undertook initial analyses independently and wrote separate reports before meeting to discuss their interpretations and reach agreement on key findings and themes. A coding frame was then developed that captured these findings and themes. NVivo Version 10 (QSR International Pty Ltd., Doncaster, Victoria, Australia), a qualitative software package, was used to facilitate data coding and retrieval, and coded data sets were subjected to further analyses to allow more nuanced interpretations of the data to be developed and identify subthemes and illustrative quotations. To safeguard anonymity, unique identifiers are used in the reporting of data that follows.

Results

Ten adults (aged 18+ years), five adolescents (aged 13–17 years), and nine parents of pediatric patients were interviewed. Demographic details of these 24 participants are presented in Table 1.

Participants, in their post-trial interviews, described having being stoical and accepting of the requirement

Table 1. Demographic characteristics of study participants.

	Participants with type 1 diabetes ($n = 15$)	Parents of pediatric participants ($n = 9$*)
Gender (*n*)		
Male	8	2
Female	7	7
Age (*n*)		
13–17 years	5	—
18–65 years	10	9
Over 65 years	—	—
Previous CLS trial experience (*n*)	6	3
Occupation		
Professional	5	5
Semiskilled	4	2
Manual	—	1
Higher education	2	—
Secondary school	3	—
Not working/caregiver	1	1

*This includes parents who represented children aged ≤12 years ($n = 5$) and parents of children aged 13–15 ($n = 4$). In one instance, both parents of a child aged 13–15 participated in an interview.

to return the closed-loop at the end of the 3-month study period. However, while none expressed anger or resentment, and virtually all conveyed enthusiasm for taking part in further trials, participants in all groups also conveyed varying degrees of upset and distress. This included Parent 7, who described how "we cried, me and [child's name], when we had to give it back. We absolutely loved it … I absolutely feel gutted, absolutely gutted." Adult 3 also reported how:

> I was just generally frustrated. And I suppose that had an impact on my immediate family … so this week you know, I stopped yesterday. So over the past few days I have felt slightly grumpy because I didn't want to give it up. (Adult 3)

In the following, we begin by considering how (and why) participants benefited psychologically and emotionally from using a closed-loop. We also explore how participants had relaxed their diabetes management practices as a result of using this technology and became deskilled as a consequence. We do this because these kinds of experiences provide a vital context for understanding why loss of the closed-loop was experienced in physically and emotionally harmful ways. We also consider participants' clinical and support needs at the end of the trial to help address the kinds of harms experienced. As all of our main findings cut across the sample, our reporting has not been separated out according to participant groups (e.g., adults, adolescents, and parents); however, we do indicate when a particular issue was most keenly felt within one particular group.

Psychological and emotional benefits to using a closed-loop

Participants described various overlapping psychological and emotional benefits to using the closed-loop, many of which only become fully apparent after they had had direct experience of using the technology.

Respite and less worry

A central benefit, as participants noted, was that the closed-loop had enabled them to have respite from managing their (or their child's) diabetes. This included Adult 3, who likened her trial experiences to being "on a holiday" due to not having to constantly think about and make a conscious effort to keep her blood glucose levels within target ranges because the closed-loop would "soak up" and address high and low blood glucose automatically:

> It was great … it was like being on a holiday, where you can forget about your diabetes as much as possible, or just relax from it as much as possible. You know, it was nice to have a back-up that would … soak up all those extra blood sugars without me having to worry about it. (Adult 3)

Participants also described how they had worried less about hypoglycemia (low blood glucose) due to the system's ability to detect when their (or their child's) blood glucose was dropping and to suspend or reduce insulin delivery before their blood glucose went too low. This was highlighted as a particular benefit by parents, such as Parent 7, who described the closed-loop as having been "life-changing" because, for the trial's duration, they had been able to sleep at night without worrying about their pre-teenage child's safety, such as the possibility of their slipping into a diabetic coma or experiencing severe (life-threatening) hypoglycemia:

> I absolutely loved it … I can only describe it for a parent, as life-changing, 'cause I mean in the night time it's unreal. And I actually, I'd sleep the whole night, 'cause I trusted it … [because] if they [blood glucose levels] started to go low, it just literally … brought it all back up again. It was amazing. I didn't want to give it back. (Parent 7)

Improved relationships; less family conflict

Participants also reported experiencing reduced conflict within their families due to improvements in their own mood resulting from experiencing more stable blood glucose levels. As Adult 3 observed, "I was just generally less grumpy because my bloods were in target more of the time … and so everyone else benefitted from that as well." Parents also highlighted the benefits of not needing to constantly remind their child to undertake diabetes management tasks, such as frequent blood glucose testing, as this was done automatically by the continuous glucose monitor:

> There wasn't so much, you know, stress I think all the time, to remind him (teenage son): have you done a sugar test? What's happening with your sugars? I think all of that took a lot of pressure [off] our relationship, especially now … he's becoming a teenager, and he doesn't want to do a lot of things that should be still happening. (Parent 5)

Greater freedom and flexibility

It was also noted how use of the closed-loop had enabled other aspects of everyday life to become more relaxed because participants had not needed to keep routines in place to remind them (or their child) to undertake blood glucose tests and, when necessary, to make adjustments to their or their child's insulin. As

a consequence, many, including Adult 8, reflected upon how they had allowed their lives to become more "complicated'" (for instance, by increasing their participation in sports and physical activities, and eating meals at more erratic times of day) during the trial:

> You could allow your lifestyle to become complicated—because you didn't need to make these sort of adjustments and corrections all the time. And so therefore if you didn't have the closed-loop you might have chosen to simplify certain things in your life so that you didn't have those complexities. (Adult 8)

By virtue of the closed-loop's ability to address falling blood glucose before it became too low, parents of pre-teenage children also noted having permitted their child to have more freedom, including allowing them, for the first time, to attend sleepovers at friends' houses and school trips without their being present. Parents also noted ensuing lifestyle benefits to themselves, such as being able to have nights out, because they had felt confident and able to leave child under the supervision of another person, such as a friend, grandparent, or babysitter:

> For the three months [of the trial] we had a break, we could anything—or she could do anything. We could even go out with [friend] because people were happy to babysit and we were happy to let them. (Parent 7)

Similar benefits were also reported by adolescents and their parents who noted how, due to the closed-loop's ability to keep their blood glucose stable, even if they forgot to administer insulin when they ate or consumed alcohol, there had been increased willingness to allow them to go out and attend parties and other social activities with peers:

> I know for a fact that my mum and dad, say if [I] was going out, they were happy to let me because I was wearing the closed-loop and, if [I] was planning to stay at my friend's or whatever, they'd say: "Oh well, put it on before you go because, you know, when you're out you don't want to be necessarily testing your blood." And my mum and dad, you know, they felt that I was safe with the closed-loop on. (Adolescent 1)

Relaxing and loosing habits

Participants also reflected upon how, as a result of having used a technology that had done a lot of the work on their behalf, they had become "lazy," as Adult 10 put it, and had gotten out of the habit of undertaking key diabetes management practices, such as regular blood glucose testing, during the trial:

> I felt that it changed my behavior in terms of my diabetes. So it did make me relax, but I suppose not always in a good way. So, for instance, I tested my blood glucose levels less often than normal because the sensors were really accurate and it didn't feel necessary. (Adult 3)

Deskilling. In extreme cases, participants voiced concerns about having become deskilled. This included Parent 8, who noted how, after their child had reverted to their pre-trial regimen (an insulin pump), they realized that they had forgotten how to determine the size of the insulin dose they needed to administer to correct (bring down) high blood glucose:

> The hardest part was actually going back at the end to just the pump, and remembering … I actually had to ask [child's name] at one point. I was like: what do we do with this? (laughs) because I'd forgotten—like getting back into doing the corrections. (Parent 8)

Adopting bad habits. Due to the closed-loop's perceived ability to automatically address small rises in blood glucose, many participants also noted that, as a result of using it, they had gotten into "bad habits" such as no longer administering insulin when they snacked:

> And also in terms of little things like snacking that I wouldn't be so vigilant about exactly how much carbohydrate I was having—so if I was preparing the kids' tea I would just sort of like have a chip or two. Generally I would normally concentrate on exactly how many chips I was having and sort of have some insulin to go with it. But on the closed-loop system I think I didn't concentrate as hard because I assumed that the system would pick it up and would deal with the blood sugars that way round … that wasn't a good habit to get into. (Adult 3)

Withdrawal of the closed-loop

Addressing bad habits, relearning skills, and reinstating old routines

For all individuals, withdrawal of the closed-loop was also experienced as "a really big step back" (Adult 7). Specifically, participants described needing to make significant effort to address bad habits adopted during the trial, reinstate former routines, and/or relearn how to undertake some of their former diabetes management tasks. As Adult 10 noted: "I'm having to step up the amount of management I do because, having got quite used to being quite relaxed about it, I now have to be less relaxed about it." As Adult 9 similarly described:

> So I've got to try and retrain myself to make the decisions it was making for me … the only concerns really are the ones limited to my forgetfulness. And if I forget to bolus [take insulin] my sugars are going up, and I don't have a sensor to warn me they're going up. I've only got—I feel a bit ropey [unwell]. So then I'll deal with it. And if I forget to bolus … I've not got anything covering my back. I've just got to do what I think's right. Whereas the [closed-loop] actually made a lot of the smart decisions for you.

Because of the amount of effort required to relearn key diabetes self-management skills and reinstate routines to remember to undertake diabetes-management tasks, some participants likened their post-trial experiences to being "a new parent again, because it's like starting from the beginning, like we haven't had diabetes before, 'cause we relied on the closed-loop so much" (Parent 4). Indeed, some, including Adult 10, noted that "it's … more of an adjustment to come back off it [closed-loop] than it is was to go on" because of the amount of time and effort required to reinstate their pre-trial diabetes management regimens.

Increased motivation tempered by reverting to antiquated self-management tools

Several participants also described how their experiences during the trial had given them a new impetus to better manage their, or their child's, diabetes after the closed-loop had been withdrawn. Specifically, some such participants, including Adolescent 4 and Adult 6, described observing improvements in their blood glucose control while using the closed-loop, and feeling much better physically as a consequence, and, hence, wanting to maintain these improvements after the trial:

> So I've been doing my bloods like more regularly. So like I'm trying to keep it better controlled, just because I know … it feels much nicer when you do. (Adolescent 4)

> It's probably inspired me to manage it a bit better cause I kind of think I can. I can have good blood sugars. Like normally after four months of being, having really good control, I'd probably just not bother at all for a few months. I'd test like once every other day, cause I'm like: I just need a break from it all. But actually I feel like: No. It's worth making the effort and trying. So I've tested my blood sugar today twice already. (Adult 6)

However, all such participants also noted the frustrations and anxieties arising from wanting to sustain better blood glucose control, but having to revert to using what they now saw as "old school methodology" (Adult 4) and antiquated technology, which as Adolescent 5 noted, "feels like going from the latest iPhone to a brick phone."

As several individuals, including Adult 7, further reflected, use of this older and more basic technology simply could not permit them to attain the fine-tuned control they now wanted to achieve, leading them to feel a "loss of control" as a consequence:

> I've experienced very high management of my diabetes. So, in contrast, you realize just how poor the amount of information you have to make decisions is when you don't have CGM [continuous glucose monitoring] … So yeah. I guess those are the negatives … So … just having like a spot check of my blood sugars … just looks, feels a bit one dimensional … after seeing … the whole sort of graph if you like of the CGM. So you kind of think: well, I'm not really getting a lot of information. You know, is my blood sugar going up or down? And eh, you don't know that from a single measurement. So I guess, in a sense, I feel like I'm less in control. (Adult 7)

Potential physical harm

Because of their new awareness of the limitations of their old regimens and the time and effort required to reinstate former habits and skills, participants also shared their anxieties and concerns that their or their child's blood glucose control would be adversely affected after the trial:

> One of the risks is that somebody becomes very lazy. And becoming very lazy because you have the closed-loop is fantastic if your closed-loop is going to be there all the time. But becoming very lazy and then you lose the closed-loop and then end up, you know, spending another three months trying to get your [child's] sugars under control because you've now got out of the habit of tightly managing them. (Parent 5)

> I know my HbA1c [average measure of blood glucose control] is going to change … I know it's going to increase over the next three months … [because] there's so much more that I need to get back into the way of doing things. Eh, I just hope that within, by at least three months from now, I will have a grasp of what I need to do. And get it back down again. (Adult 9)

Psychological and emotional harms

The emotional and psychological impact of having to step back into a life without the closed-loop was also widely discussed. This issue is understandable given that, as described earlier, use of this technology had had such a positive impact on participants' quality of life. Specifically, participants shared their worries and concerns about having to return to their more restricted (pre-trial) lives, characterized by family conflict, worry, strain, and a more regimented way of living. This was especially the case for parents who

shared the distress resulting from having to revert to getting up several times during the night to make sure their child was not experiencing hyper- or hypoglycemia now that the closed-loop was no longer there to stop blood glucose from going high or low:

> So last night, I've been up all night. I've literally had three hours sleep. His sugars went high. Then I'm having to give him an adjustment, then having to wait. Whereas the artificial pancreas, the whole three months he had it, he had one hypo in the night … I actually thought: I can't even believe that I'm having to go back to this after having—it was like luxury. (Parent 9)

Indeed, Parent 9's implied grief was more explicitly articulated by others, including Parent 7, who likened their experience of losing the closed-loop to that of losing a family member:

> We need to get used to it again, not sleeping … You get used to sleeping, and suddenly you aren't sleeping again and [yawns] here we go again … We just—we just really liked it, and really miss it now. So I think we feel like we lost a member of our family.

Adults and adolescents also shared their sense of loss and emotional distress. This included Adult 4, who described having been "so much happier when I was on it [closed-loop] because it took so much of the stress away of having diabetes" and noted how they now felt like "a part of you is missing in some ways because, for me, using the closed-loop was life changing, so I really didn't want to give it back."

When they reflected upon the emotional impact of returning the closed-loop at the end of the trial, some participants, including Parent 3, also noted how, by virtue of having had such positive experiences while using it, they now saw the life to which they (or their child) had to return much more negatively:

> The study gave him a taste [of] what it feels like to have a working artificial pancreas … as with all the studies you know, you have that period where it's all finished and you have to go back to how it was. And therefore it's almost like taking a glimpse to what the future would look like. And then you go back again. And I think, you know, that is hard. (Parent 3)

Support received and needed at the end of the trial

Virtually all participants indicated a need for support after completing the trial, with Adult 8, among others, noting that, had support from staff been abruptly withdrawn, this would have had a very detrimental impact:

> If my consultant said: right, thank you very much. Delete my number. Delete my email address. We aren't having any more contact. That would not work. It—your—your sugars are going to go absolutely haywire afterwards.

Most individuals highlighted a need for clinical and educational input to help them relearn and reinstate pre-trial treatment regimens. However, some also indicated needing more holistic support, which comprised psychological as well as clinical elements. This was not only to help address anxieties and distress resulting from withdrawal of the closed-loop, but also to help them regain their confidence managing their or their child's diabetes without the input of the closed-loop:

> Now I feel less confident. I just—last night was completely like I'm mind crazy … there's an e-mail gone to [the hospital at] two o'clock in the morning going: help me, as I just needed someone to reassure me that everything is going to be ok and that I am doing things right. (Parent 7)

While there was no protocol or ethically mandated requirement for trial staff to offer post-trial support, all participants described how staff had emphasized and reassured them of their ongoing availability. However, it was also noted that, because this offer of post-trial support had been informal and unstructured, the onus had been placed on them to initiate contact (by e-mail or phone) and "bother the doctor" (Adult 2) in the event that they felt they needed help:

> They did say it [blood glucose levels] might for the first few days be a bit erratic … but if I was quite worried to then just get in touch … and they'll talk me through bits and pieces I can do. (Adult 2)

Hence, participants suggested that that future trial participants would benefit from more formal arrangements, whether this be a post-trial debriefing and education session as suggested by Parent 3, or, in Adult 7's case, a series of contacts with staff to allow them time to optimize their blood glucose control using the pre-trial regimens to which they had had to revert:

> A session with the team, where you would say … here's the devices. Here's everything back. Here is what we will suggest [you do with] your basal rates. But this is something to remind us now that you do need to do a little bit more testing and … that system is not there anymore for you. (Parent 3)

> I think it would quite useful to maybe get another one or two weeks with [health professional] contact … because the three months is quite a while … so having the extra assistance … even if it's just for two weeks, you can get your sugars back into check. (Adult 7)

Discussion

This study has offered an empirical window into an area of growing ethical attention and debate: whether

individuals who take part in trials should be given opportunities to access post-trial care and what this care should comprise. In this study, which drew upon the perspectives and experiences of individuals (adults, adolescents, and parents) who had just completed a trial of an innovative technology to support management of type 1 diabetes, participants in all groups highlighted a need for post-trial care and support. In part, this support was seen as necessary to help circumvent potential physical harms (a deterioration in blood glucose control) arising from withdrawal of the closed-loop. Specifically, individuals described wanting and valuing education, training, and practical support from trial staff to help reinstate the (forgotten) skills, habits, and routines needed to undertake effective diabetes self-management using the regimens to which they had to revert. Mirroring findings from other studies involving users of closed-loop systems, participants also described experiencing nonclinical benefits during the trial because the closed-loop had lessened the burden of diabetes management; permitted a more spontaneous and flexible lifestyle; and reduced worry and enabled improved sleep, especially among parents (Barnard et al. 2014, 2015; Hendrieckx et al. 2017). Hence, for these individuals, trial participation had unanticipated consequences for which they had felt ill-prepared and that had not been discussed in the participant information sheet (see earlier discussion). Specifically, participants experienced a better (quality of) life that could not be sustained once the closed-loop had been withdrawn. Participants also described having reevaluated their pre- and post-trial life in light of using a closed-loop and noted how they now perceived this life more negatively. Others voiced frustrations about wanting to maintain the improvements in blood glucose control that had resulted from using the closed-loop, but of having to revert to using what they now saw as technologically imprecise self-management tools. Understandably, therefore, while participants were accepting of the requirement to return the closed-loop, virtually all described experiencing disappointment, anxiety, and a sense of loss. In doing so, participants highlighted both implicit and explicit needs for psychological and emotional support from staff. Hence, one contribution of this study is that it highlights the importance of debates about the provisioning of post-trial care being extended to trials of medical devices. We would also argue that these kinds of debates need to be widened: specifically, that the kinds of harms considered in the ethical literature about post-trial care provisioning (e.g., Cook, Snyder, and Calvert 2016; Doval, Shirali, and Sinha 2015; Grady 2005; Millum 2011) need to be broadened to consider potential emotional and psychological harms, and not just clinical harms, which may result from withdrawal of trialed treatments.

In this study, participants did feel well supported by staff after trial completion and were grateful for their ongoing availability. However, because care arrangements had been informal and unstructured, individuals had felt the onus had been on them to initiate contact. This lack of formal post-trial support is unsurprising given that, as others have noted, even in situations where post-trial obligations have been seen to exist (e.g., UNAIDS: Joint United Nations Programme on HIV/AIDS 2011; World Health Organization, and Council for International Organizations of Medical Sciences 2016), it often remains unclear with whom the moral and ethical duty resides to provide post-trial care (usually ongoing access to drugs) (Doval, Shirali, and Sinha 2015; Grady 2005; Millum 2011; Pratt and Loff 2011; Sofaer et al. 2009). Commentators have also suggested that this responsibility should not fall upon the investigator team but, rather, should be cascaded to governments, sponsors, and, in some cases, the international community (Millum 2011); indeed, the 2013 version of the Declaration of Helsinki acknowledges that the burden of providing post-trial access to treatment is far beyond the investigators' scope (Palacios 2013). Commentators have also noted a lack of clarity about how post-trial care should be delivered to ensure ethical responsibilities are met (Andanda and Wathuta 2018). This includes Cook, Snyder, and Calvert (2016), who, in a recent review of academic literature, legislation, and international guidelines, note a distinct paucity of practical and tangible recommendations for addressing post-trial provisioning. As these authors further suggest, this tendency to make general rather than specific recommendations may serve to "mask the underlying challenges by providing cosmetic improvements to existing practices" (Cook, Snyder, and Calvert 2016, 76). Pratt and Loff (2011) have raised similar concerns and, in doing so, have highlighted the dangers of macro-level obligations being allocated to micro-level actors. In keeping with these kinds of ethical concerns, others have noted how, in the absence of specific guidelines, resourcing, and formal oversight, it has tended to fall to local investigators and front-line staff to creatively seek out temporary solutions to meet individuals' post-trial needs, even though they have no formal ethical mandate to do so. This might include identifying additional research protocols in order to continue to

provide participants with beneficial drugs (Grady 2005) or, in the case of the current study, providing clinical, educational, and emotional support to help individuals adjust to the loss of the closed-loop and reinstate pre-trial regimens.

Although offers of post-trial support were appreciated by participants, other research, like our own, suggests that individuals may be reluctant to initiate contact with health professionals due to their concerns that these individuals are already overstretched (Rankin et al. 2012). In other words, when offers of health professional support are informal, participants may not always access the care they need. The impact on front-line staff also needs to be considered. As research undertaken with staff involved in the close-out of another diabetes trial entailing withdrawal of treatment (insulin pumps) has served to highlight, ethical and emotional challenges at close-out may also extend to front-line staff (Lawton et al. 2017). In this study, staff members reported feeling ill-prepared for close-out and, more specifically, for withdrawing treatment from patients who were anxious and distressed (Lawton et al. 2017). Staff members also felt ill-equipped to provide patients with the emotional and psychological support some needed due to lack of resourcing and appropriate training. This study concluded that the close-out of trials involving withdrawal of treatments/technologies should be subjected to the same level of ethical oversight as trial recruitment and delivery stages, a recommendation echoed by others who have also suggested that the remit of ethics committees should be broadened to help ensure ethically appropriate post-trial provisioning takes place (Andanda and Wathuta 2018; Grady 2005). As well as increased ethical oversight, staff members working on future trials of medical devices might benefit from being given training and resourcing as part of their core trial funding to ensure they are able to give patients the support they need following treatment withdrawal. This might include input from psychologists, so that the kinds of emotional distress reported by participants in the current study, and noted by staff in the study where insulin pumps were withdrawn (Lawton et al. 2017), are handled appropriately. Our findings also suggest that, in order to help make informed decisions about their participation, individuals who are approached to take part in future trials might also benefit from being given information about potential (nonclinical) harms arising from withdrawal of treatment.

While the current study raises important questions about what constitutes harm at the end of trials involving withdrawal of treatment, the specifics of the trial need to be taken into account. First, it needs to be considered that the trial's investigated technology was not commercially available; this made post-trial provisioning a moot issue, as current regulations in the United Kingdom do not permit compassionate use of (expanded access to) nonapproved medical devices outside a clinical trial. It should also be noted that, in comparison to individuals in Third World and low-income settings who might have to confront withdrawal of a potentially lifesaving or sustaining treatment without an alternative treatment being made available, participants in the current study were able to return to a regimen that has been shown to be clinically effective (REPOSE Study Group 2017). Hence, it is likely that the kinds of emotional distress reported in this article might be even greater in other kinds of settings and trials. The relatively short duration (3 months) participants were in the trial should also be taken into account. While participants described their anxieties about having become deskilled as a result of using the closed-loop, it is likely that this deskilling and, hence, participants' distress and need for post-trial support would have been greater in a trial of longer duration. Others have also noted that in long-term trials, participants may build up special relationships with researchers, and hence they may experience termination of these relationships as a form of betrayal (Sofaer et al. 2009). In other words, risks of emotional harm may not just arise from withdrawal of treatment but also from withdrawal of relationships forged during long-term trials. Empirical support for this suggestion can be found in a study in which individuals were interviewed after taking part in a diabetes trial that lasted more than 20 years. These individuals described having forged close relationships with trial staff members over the years, and hence of having experienced a form of bereavement when the trial came to an end (Lawton et al. 2003).

Study limitations

As is typical in trials of technological innovations and medical devices (e.g., Polonsky and Hessler 2013; Ritholz et al. 2010), our sample was heavily skewed toward well-educated individuals belonging to higher socioeconomic groups, and this potentially limits the applicability of our findings. While we have provided an in-depth understanding of what the ethical issues are for trial participants when treatment (a medical device) is withdrawn at the end of the trial, our study would have been enhanced by longer term follow-up of participants to establish the full implications of the

emotional, psychological, and physical harms they reported at trial close-out.

Conclusion

This article has reported findings from interviews undertaken with individuals who took part in a trial which sought to advance a technology that is intended to have a very direct and meaningful impact on the health and well-being of people affected by type 1 diabetes (Bekiari et al. 2018). Despite the beneficent nature of this trial being only too apparent, and the study undergoing all the required peer-review processes and ethical and research governance approvals, we have shown that there was potential for participants to experience (unanticipated) harms at the end of the trial by virtue of treatment withdrawal, although it would appear that these harms were mitigated by local investigators offering informal, post-trial support. Not only does this study highlight the need for ethical consideration and debates to move beyond drugs trials undertaken in low-income settings; we have also shown that for these debates to be responsible, understandings of harm may need to be broadened to consider psychological and emotional harms, as well potential clinical harm, which may result from withdrawal of trial treatments. We have also suggested that, to help make informed decisions about their participation, individuals might benefit from being given information about these kinds of nonclinical harms.

Acknowledgments

We thank all of the individuals who took part in the interview study and the health professionals who assisted with recruitment. Josephine Hayes, University of Cambridge, provided administrative support and was the study coordinator.

Author contributions

JL designed the study, analyzed the data, and drafted the article. MB conducted the interviews and contributed to the analysis of the data. DR contributed to the analysis of the data and helped draft the article. CW contributed to the analysis of the data and helped draft the article. CF contributed to the interpretation of the data and helped draft the article. RH was involved in the conception and design of the study and helped draft the article. NH contributed to the interpretation of the data and helped draft the article.

Funding

Closed-loop research at Cambridge is supported by JDRF, National Institute for Health Research Cambridge Biomedical Research Centre, National Institute of Diabetes and Digestive and Kidney Diseases, Horizon 2020, Helmsley Trust, and a Wellcome Strategic Award (100574/Z/12/Z).

Conflicts of interest

Roman Hovorka reports having received speaker honoraria from Eli Lilly and Novo Nordisk, serving on advisory panel for Eli Lilly and Novo Nordisk, and receiving license fees from BBraun and Medtronic. Roman Hovorka also reports patents and patent applications. All the other authors have no conflicts to declare.

Ethical approval

This study was approved by the institutional review board(s) at Cambridge East Research Ethics Committee (REC ref 15/EE/0324

ORCID

J. Lawton http://orcid.org/0000-0002-8016-7374
C. Werner http://orcid.org/0000-0003-2989-096X
R. Hovorka http://orcid.org/0000-0003-2901-461X

References

Andanda, P., and J. Wathuta. 2018. Human dignity as a basis for providing post-trial access to healthcare for research participants: A South African perspective. *Medicine, Health Care and Philosophy* 21 (1):139–55. doi: 10.1007/s11019-017-9782-1.

Ballantyne, A. 2008. Fair benefits' accounts of exploitation require a normative principle of fairness: Response to Gbadegesin and Wendler, and Emanuel et al. *Bioethics* 22 (4):239–44. doi: 10.1111/j.1467-8519.2007.00622.x.

Bally, L., H. Thabit, M. Tauschmann, J. M. Allen, S. Hartnell, M. E. Wilinska, J. Exall, V. Huegel, J. Sibayan, and S. Borgman. 2017. Assessing the effectiveness of a 3-month day-and-night home closed-loop control combined with pump suspend feature compared with sensor-augmented pump therapy in youths and adults with suboptimally controlled type 1 diabetes: A randomised parallel study protocol. *BMJ Open* 7 (7):e016738. doi: 10.1136/bmjopen-2017-016738.

Barnard, K. D., T. Wysocki, J. M. Allen, D. Elleri, H. Thabit, L. Leelarathna, A. Gulati, M. Nodale, D. B. Dunger, T. Tinati., et al. 2014. Closing the loop overnight at home setting: Psychosocial impact for adolescents with type 1 diabetes and their parents. *BMJ Open Diabetes Research & Care* 2 (1):e000025. doi: 10.1136/bmjdrc-2014-000025.

Barnard, K. D., T. Wysocki, H. Thabit, M. L. Evans, S. Amiel, S. Heller, A. Young, and R. Hovorka. 2015. Psychosocial aspects of closed- and open-loop insulin

delivery: Closing the loop in adults with type 1 diabetes in the home setting. *Diabetic Medicine* 32 (5):601–8. doi: 10.1111/dme.12706.

Bekiari, E., K. Kitsios, H. Thabit, M. Tauschmann, E. Athanasiadou, T. Karagiannis, A. Haidich, R. Hovorka, and A. Tsapas. 2018. Artificial pancreas treatment for outpatients with type 1 diabetes: Systematic review and meta-analysis. *British Medical Journal* 361:k1310.

Cook, K., J. Snyder, and J. Calvert. 2016. Attitudes toward post-trial access to medical interventions: A review of academic literature, legislation, and international guidelines. *Developing World Bioethics* 16 (2):70–9. doi: 10.1111/dewb.12087.

Doval, D. C., R. Shirali, and R. Sinha. 2015. Post-trial access to treatment for patients participating in clinical trials. *Perspectives in Clinical Research* 6 (2):82–5. doi: 10.4103/2229-3485.154003.

Emanuel, E. J., D. Wendler, and C. Grady. 2000. What makes clinical research ethical? *Journal of the American Medical Association* 283 (20):2701–11. doi: 10.1001/jama.283.20.2701.

El Setouhy, M., T. Agbenyega, F. Anto, C. A. Clerk, K. A. Koram, M. English, C. Molyneux, N. Peshu, R. Juma, N. Kumwend., et al. 2002. Fair benefits for research in developing countries: Participants in the 2001 conference on ethical aspects of research in developing countries. *Science* 298(5601):2133–4. doi: 10.1126/science.1076899.

Grady, C. 2005. The challenge of assuring continued post-trial access to beneficial treatment. *Yale Journal of Health Policy, Law, and Ethics* 5 (1):425–35.

Hendrieckx, C., L. A. Poole, A. Sharifi, D. Jayawardene, M. M. Loh, J. C. Horsburgh, L. A. Bach, P. G. Colman, K. Kumareswaran, A. J. Jenkins., et al. 2017. It is definitely a game changer": A qualitative study of experiences with in-home overnight closed-loop technology among adults with type 1 diabetes. *Diabetes Technology & Therapeutics* 19 (7):410–6. doi: 10.1089/dia.2017.0007.

Lawton, J., A. Fox, C. Fox, and A. L. Kinmonth. 2003. Participating in the United Kingdom prospective diabetes study (UKPDS): A qualitative study of patients' experiences. *British Journal of General Practice* 53 (490):394–8.

Lawton, J., D. White, D. Rankin, J. Elliott, C. Taylor, C. Cooper, S. Heller, and N. Hallowell. 2017. Staff experiences of closing out a clinical trial involving withdrawal of treatment: Qualitative study. *Trials* 18 (1):61. doi: 10.1186/s13063-017-1813-y.

Lawton, J., M. Blackburn, J. Allen, F. Campbell, D. Elleri, L. Leelarathna, D. Rankin, M. Tauschmann, H. Thabit, and R. Hovorka. 2019a. The impact of using a closed-loop system on food choices and eating practices amongst people with type 1 diabetes: A qualitative study involving adults, teenagers and parents. *Diabetic Medicine*. DOI: https://doi.org/10.1111/dme.13887.

Lawton, J., M. Blackburn, J. Allen, F. Campbell, D. Elleri, L. Leelarathna, D. Rankin, M. Tauschmann, H. Thabit, and R. Hovorka. 2019b. Participants' experiences of, and views about, daytime use of a hybrid closed-loop system in real life settings: Longitudinal qualitative study. *Diabetes Technology & Therapeutics* 21 (3):119–27. https://doi.org/10.1089/dia.2018.0306.

Lawton, J., N. Waugh, K. Barnard, K. Noyes, J. Harden, J. Stephen, J. McDowell, and D. Rankin. 2015. Challenges of optimizing glycaemic control in children with type 1 diabetes: A qualitative study of parents' experiences and views. *Diabetic Medicine* 32 (8):1063–70. doi: 10.1111/dme.12660.

Macklin, R. 2004. *Double standards in medical research in developing countries*. Cambridge, UK: Cambridge University Press.

Merritt, M., and C. Grady. 2006. Reciprocity and post-trial access for participants in antiretroviral therapy trials. *Aids* 20 (14):1791–4. doi: 10.1097/01.aids.0000244197.88134.45.

Millum, J. 2011. Post-trial access to antiretrovirals: Who owes what to whom? *Bioethics* 25 (3):145–54. doi: 10.1111/j.1467-8519.2009.01736.x.

Pace, C., C. Grady, D. Wendler, J. D. Bebchuk, J. A. Tavel, L. A. McNay, H. P. Forster, J. Killen, and E. J. Emanuel. 2006. Post-trial access to tested interventions: The views of IRB/REC chair, investigators, and research participants in a multinational HIV/AIDS study. *AIDS Research & Human Retroviruses* 22 (9):837–41. doi: 10.1089/aid.2006.22.837.

Palacios, R. 2013. Post-trial access and the new version of the declaration of Helsinki. *Colombia Medica (Cali, Colombia)* 44 (4):206–7.

Petryna, A. 2009. *When experiments travel*. Princeton: Princeton University Press.

Polonsky, W. H., and D. Hessler. 2013. What are the quality of life-related benefits and losses associated with real-time continuous glucose monitoring? A survey of current users. *Diabetes Technology & Therapeutics* 15 (4):295–301. doi: 10.1089/dia.2012.0298.

Poolsup, N., N. Suksomboon, and A. M. Kyaw. 2013. Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. *Diabetology & Metabolic Syndrome* 5 (1):39. doi: 10.1186/1758-5996-5-39.

Pope, C., and N. Mays. 1995. Qualitative research: Reaching the parts other methods cannot reach: An introduction to qualitative methods in health and health services research. *British Medical Journal* 311 (6996):42–5. doi: 10.1136/bmj.311.6996.42.

Pratt, B., and B. Loff. 2011. Justice in international clinical research. *Developing World Bioethics* 11 (2):75–81. doi: 10.1111/j.1471-8847.2010.00296.x.

Rankin, D., D. D. Cooke, J. Elliott, S. R. Heller, and J. Lawton. 2012. Supporting self-management after attending a structured education programme: A qualitative longitudinal investigation of type 1 diabetes patients' experiences and views. *BMC Public Health* 12 (1):652. doi: 10.1186/1471-2458-12-652.

REPOSE Study Group. 2017. Relative effectiveness of insulin pump treatment over multiple daily injections and structured education during flexible intensive insulin treatment for type 1 diabetes: Cluster randomised trial (REPOSE). *British Medical Journal* 356:j1285.

Ritholz, M. D., A. Atakov-Castillo, M. Beste, E. A. Beverly, A. Leighton, K. Weinger, and H. Wolpert. 2010. Psychosocial factors associated with use of continuous glucose monitoring. *Diabetic Medicine* 27 (9):1060–5. doi: 10.1111/j.1464-5491.2010.03061.x.

Shaffer, D. N., V. N. Yebei, J. B. Ballidawa, J. E. Sidle, J. Y. Greene, E. M. Meslin, S. J. N. Kimaiyo, and W. M. Tierney.

2006. Equitable treatment for HIV/AIDS clinical trial participants: A focus group study of patients, clinician researchers, and administrators in western Kenya. *Journal of Medical Ethics* 32 (1):55–60. doi: 10.1136/jme.2004.011106.

Sofaer, N., C. Thiessen, S. D. Goold, J. Ballou, K. A. Getz, G. Koski, R. A. Krueger, and J. S. Weissman. 2009. Subjects' views of obligations to ensure post-trial access to drugs, care and information: Qualitative results from the experiences of participants in clinical trials (EPIC) study. *Journal of Medical Ethics* 35 (3):183–8. doi: 10.1136/jme.2008.024711.

Sofaer, N., and D. Strech. 2011. Reasons why post-trial access to trial drugs should, or need not be ensured to research participants: A systematic review. *Public Health Ethics* 4 (2):160–84. doi: 10.1093/phe/phr013.

Strauss, A., and J. M. Corbin. 1990. *Basics of qualitative research: Grounded theory procedures and techniques*. London: Sage Publications, Inc.

UNAIDS: Joint United Nations Programme on HIV/AIDS. 2011. *Good participatory practice: Guidelines for biomedical HIV prevention trials*. Accessed November 12, 2018. http://www.unaids.org/sites/default/files/media_asset/JC1853_GPP_Guidelines_2011_en_0.pdf.

Usharani, P., and S. M. H. Naqvi. 2013. Post-trial access. *Perspectives in Clinical Research* 4 (1):58–60. doi: 10.4103/2229-3485.106391.

Williams, C. 2000. Doing health, doing gender: Teenagers, diabetes and asthma. *Social Science & Medicine* 50 (3): 387–96. https://doi.org/10.1016/S0277-9536(99)00340-8. doi: 10.1016/S0277-9536(99)00340-8.

World Health Organization, and Council for International Organizations of Medical Sciences. 2016. *International ethical guidelines for health-related research involving humans*. Geneva: Council for International Organizations of Medical Sciences. Available at https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf.

World Medical Association. 2000. Declaration of Helsinki, ethical principles for medical research involving human subjects. *Journal of the American Medical Association* 284 (23):3043–5. doi: 10.1001/jama.284.23.3043.